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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,807	02/27/2004	Benjamin Tjoa	020093-003710US	5631

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
JUEDES, AMY E	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,807	TJOA ET AL.	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *4-7,10-12,16 and 24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,9,13-15,and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/28/04, 3/4/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: notice to comply

DETAILED ACTION

1. Applicant's amendment, filed 10/26/05, is acknowledged.

Claims 25-29 have been added.
Claims 1-29 are pending.

2. Applicant's species election, in the reply filed 10/26/05 is acknowledged. Applicant has elected a low avidity culture flask comprising PFTE as the species of inhibiting adhesion and BCG and IFN-γ as the species of dendritic cell maturation agent. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant states that Claims 1-3, 8-9, 13-15, and 17-29 read on the elected species. However, it is noted that Claim 24 depends on claim 10, which is drawn to a non-elected species (i.e. inhibiting adhesion with protein). Furthermore, newly added claims 25-29 are drawn to inhibiting adhesion with a combination of a low avidity culture vessel and a high concentration of protein. This represents an additional species of the claimed invention that was not part of the original claims. Therefore, Claims 4-7, 10-12, 16, and 24-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Claims 1-3, 8-9, 13-15, and 17-23 read on the elected invention and are being acted upon.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reason(s) set forth below:

The application contains amino acid sequences (see SEQ ID NOS: 1 and 2 on pg. 16 of the specification), however no sequence listing has been provided. Applicant is required to submit a CRF, Sequence Listing, and Statement that the contents are identical.

4. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the

material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter into this application by reference to WO2004/000444 is improper because it is apparent that the tangential flow filtration procedure is essential to practice the claimed invention.

5. The use trademarks has been noted in this application (e.g. TEFLON™, on pg. 11 and PLASBUMIN™, on page 22). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. Claims 18 and 21 are objected to because of the following informalities: Claim 18 is partially written in the past tense (i.e. the filtration rate was 17ml/min). Applicant is required to phrase claims in the present tense. Additionally, Claim 21 states that a maturation agent "comprises is" BCG. Appropriate correction is required.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear, and hence indefinite, how a method that requires the "absence of additional cytokines" can also employ IFN-γ.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear,

> concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could function as a method for differentiating precursors into immature dendritic cells.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable.

The specification provides insufficient data to enable claims drawn to the method as claimed. It is noted that the

claimed invention is drawn to a method of differentiating precursors into immature dendritic cells. It is also noted that the method steps of Claims 20-21 involve contacting the differentiated precursors with a maturation agent, such as BCG and IFN-γ. As evidenced by Bosch et al., 2001, J. Invest. Derm., BCG and IFN-γ are potent inducers of DC maturation. Therefore, it is evident to one of ordinary skill in the art that a method that involves contacting differentiated precursors with the maturation agents BCG and IFN-γ would result in a mature dendritic cell, and not an immature dendritic cell, as claimed. Accordingly, the method as claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 14, 19, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Sallusto et al., 1994, J. Exp. Med.

Sallusto teaches a method for generating dendritic cells from peripheral blood mononuclear cells (i.e. monocytic dendritic cell precursors) by culturing in GM-CSF in the absence of additional cytokines (see Table 1). Furthermore, said dendritic cells are immature, as evidenced by their expression of CD11c and MHC, but lack of expression of B7 (see Table 1). Furthermore, the monocytic dendritic cell precursors used to generate the immature dendritic cells were non-activated (i.e. isolated on a Percoll gradient without positive selection or other stimulation- see materials and methods). Additionally, the differentiated dendritic cells were contacted with a bacterial antigen (tetanus toxoid) for a time period sufficient for antigen uptake, as evidence by their ability to stimulate tetanus toxoid specific T cells (see Table 1).

Thus, the reference clearly anticipates the invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 3 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto et al., 1994, J. Exp. Med, in view of Bernard et al., 1998, Hem. Cell. Ther.

The teachings of Sallusto are described above.

Sallusto does not culture in a low avidity culture vessel comprising PFTE.

Bernard teaches a method to generate dendritic cells from purified blood monocytes by culturing in a TEFLON^{tm} (i.e. comprising PFTE) bag. Furthermore, Bernard teaches that said method meets good laboratory practice (GLP) procedures necessary for the clinical use of dendritic cells (see pg. 23).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using the TEFLON^{tm} culture vessel, as taught by Bernard. The ordinary artisan at the time the invention was made would have been motivated to do so, since Bernard teaches that this method is useful for clinical purposes, since it involves the large scale differentiation of dendritic cells in a culture system that meets GLP procedures (see abstract and pg. 23). Moreover, one of ordinary skill in the art would have a reasonable expectation of success.

12. Claim 13 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto et al., 1994, J. Exp. Med, in view of Bosch et al., 2001, J. Invest. Derm., meeting abstract.

The teachings of Sallusto are described above.

Sallusto does not teach generating immature dendritic cells in serum free medium, nor maturing dendritic cells with IFN-γ and BCG.

Bosch teaches that dendritic cells can be successfully generated in serum free medium, and that dendritic cells can be matured with a combination of INF-γ and BCG. Furthermore, Bosch teaches that dendritic cells are extremely useful for therapeutic purposes, and that the serum free culture medium (in contrast to the FBS containing medium taught by Sallusto) complies with the good manufacturing practice conditions that are required for clinical trials. Additionally, Bosch teaches that maturation with IFN-γ and BCG results in a dendritic cell population that can induce a immune response against a tumor antigen in cancer patients (i.e. a therapeutically useful dendritic cell population).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using serum free medium, as taught by Bosch. The ordinary artisan at the time the invention was made would have been motivated to use serum free medium, since Bosch teaches that dendritic cells are extremely useful for therapeutic purposes, and that the serum free culture medium (in contrast to the FBS containing medium taught by Sallusto) complies with the good manufacturing practice conditions that are required for clinical trials. Furthermore, it would have been obvious to one of ordinary skill in the art to mature the dendritic cells, as taught by Sallusto, with BCG and IFN-γ as taught by Bosch. The ordinary artisan would have been motivated to do so, since Bosch teaches that IFN-γ and BCG are extremely potent maturation agents that result in a dendritic cell population that can induce a immune response against a tumor antigen in cancer patients (i.e. a therapeutically useful dendritic cell population). Moreover, one of ordinary skill in the art would have a reasonable expectation of success, since Bosch teaches the effectiveness of these techniques in the generation of dendritic cells.

13. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto et al., 1994, J. Exp. Med, in view of Lewalle et al., 2000, J. Immunol. Methods.

The teachings of Sallusto are described above.

Sallusto does not teach using a cryopreserved cell population to generate dendritic cells.

Lewalle teaches the generation of dendritic cells from frozen peripheral blood mononuclear cells (see pg. 70). Furthermore, Lewalle teaches that many clinical protocols are based on sequential injections of dendritic cells, and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes (see pg. 70).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using frozen peripheral blood mononuclear cells, as taught by Lewalle. The ordinary artisan at the time the invention was made would have been motivated to do so, since Lewalle teaches that many clinical protocols are based on sequential injections of dendritic cells (see pg. 70), and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes. Furthermore, the ordinary artisan would have had a reasonable expectation of success, since Lewalle teaches that dendritic cells derived from frozen peripheral blood mononuclear cells retain their functional capacity (see pg. 73).

14. Claims 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sallusto et al., 1994, J. Exp. Med, in view of US patent application publication 20050173315.

The teachings of Sallusto are described above.

Sallusto does not teach enriching dendritic cell precursors by tangential flow filtration.

The '315 application teaches a method to enrich monocytes (i.e. dendritic cell precursors) from blood by tangential flow filtration (see paragraph 13). Furthermore, the '315 teaches using a filter size of 5.5 microns (see paragraph 49), a recirculation rate of 1680 ml/min (i.e. about 1400), a filtration rate of 15 ml/min (i.e. about 17), and a filtration time of 90 min (see example 7). Furthermore, the '315 application teaches that the tangential flow filtration method is advantageous since it eliminates laborious washing and

centrifugation steps that can lead to decreased cell viability (see paragraph 4).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immature dendritic cell, as taught by Sallusto, using monocytes enriched by tangential flow filtration, as taught by the '315 application. The ordinary artisan at the time the invention was made would have been motivated to do so, since the '315 application teaches that the tangential flow filtration method is advantageous since it eliminates laborious washing and centrifugation steps that can lead to decreased cell viability (see paragraph 4). Furthermore, the ordinary artisan would have had a reasonable expectation of success, since the '315 application teaches that dendritic cells can be successfully derived from monocytes isolated by tangential flow filtration (see example 8).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amy E. Juedes, Ph.D.
Patent Examiner
Technology Center 1600
November 7, 2005

12/8/05
G.R. EWOLDT, PH.D.
PRIMARY EXAMINER

Notice to Comply	Application No. 10/789,807	Applicant(s) Tjoa et al.	
	Examiner Amy E. Juedes, Ph.D.	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
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